Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
396-1PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/007168	01.07.2004	03.07.2003

International Patent Classification (IPC) or national classification and IPC

A61K31/343, A61K31/352, A61P15/16, A61P15/18

Applicant

NEYSES, Ludwig

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/007168

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-11 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 1-11 received by this Authority on 02.05.2005 with letter of 02.05.2005

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets 1/3-3/3 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/007168

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1,2,5-10 (in part);3,4,11;1,2,5-7 ()

because:

☒ the said international application, or the said claims Nos. 1,2,5-7
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See Supplemental Box

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 1,2,5-10(in part); 3,4,11 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/007168

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted the claims nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1,2,5-10 (in part)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/007168

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 2, 5-7, 9-10	YES
	Claims	8	NO
Inventive step (IS)	Claims		YES
	Claims	1, 2, 5-10	NO
Industrial applicability (IA)	Claims	8-10	YES
	Claims	1, 2, 5-7 (see supplemental box)	NO

2. Citations and explanations (Rule 70.7)

1. The applicant's attention is drawn to the fact that the examination report is established only in respect of that part of the subject matter of the application for which an international search report was established (PCT Rule 66.1(e)). Consequently, in the opinion of the Examining Authority, the present report concerns only the use of 5- and 6-carboxyeosin diacetate-succimidyl esters for the purpose of contraception.

2. The present international preliminary examination report refers to the following documents:

D1: KANWAR U ET AL: "GOSSYPOL INHIBITION OF CA++ UPTAKE AND CA++- ATPASE IN HUMAN EJACULATED SPERMATOZOAL PLASMA MEMBRANE VESICLES" CONTRACEPTION, GERON-X, INC., LOS ALTOS, CA, US, Vol. 39, No. 4, 1 April 1989 (1989-04-01) pages 431-445, XP000561575 ISSN: 0010-7824

D2: BREITBART H ET AL: "THE ROLE OF CALCIUM AND CA2+- ATPASE IN MAINTAINING MOTILITY IN RAM SPERMATOZOA" JOURNAL OF BIOLOGICAL CHEMISTRY. (MICROFILMS), AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS,

BALTIMORE, MD, US, Vol. 260, No. 21, 25 September 1985 (1985-09-25), pages 11548-1153, XP001009929

D3: PATNI ANIL K ET AL: "Role of intracellular calcium in the spermicidal action of 2',4'-dichlorobenzamil, a novel contact spermicide" JOURNAL OF PHARMACY AND PHARMACOLOGY, Vol. 53, No. 10, October 2001 (2001-10), pages 1387-1392, XP008036557 ISSN: 0022-3573

D4: SCHUH KAI ET AL: "The sarcolemmal calcium pump PMCA: An effector of platelet aggregation." CIRCULATION, Vol. 106, No. 19 Supplement, 5 November 2002 (2002-11-05), pages II-79, XP008036566 & ABSTRACTS FROM SCIENTIFIC SESSIONS; CHICAGO, IL, USA; NOVEMBER 17-20, 2002 ISSN: 0009-7322.

Novelty

3.1 Claims 1, 2, 5-7, 9 and 10 of the present application satisfy the requirements of PCT Article 33(1) because the subject matter of these claims is novel within the meaning of PCT Article 33(2).

3.2 Document D4 discloses the compound claimed in claim 2, carboxyeosin diacetate succimidyl ester, as PMCA (plasma membrane calcium-ATPase) inhibitor and its use as incubating agent. A composition containing the claimed compound is therefore already disclosed in document D4.

Consequently, the subject matter of claim 8 is not novel within the meaning of PCT Article 33(2).

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Inventive step

4. Document D2 is considered the prior art closest to the subject matter of the claims. According to document D2 the plasma membrane calcium-ATPase is responsible for sperm motility. Quercetin inhibits this plasma membrane ATPase, as well as sperm motility.

According to document D3, benzamil inhibits calcium-ATPase. Compounds of benzamil and propanolol (a further contraceptive) are synergistic spermicides and completely immobilize sperm.

Consequently, the subject matter of these claims differs from that known from documents D2 and D3 in that different compounds are used to inhibit sperm motility, for example inhibitors of the plasma membrane calcium-ATPase (PMCA), the inhibitor being directed against the isoform PMCA4.

The problem to be solved by the present invention is therefore understood to be that of developing alternative contraceptive compounds.

The solution proposed in the present application cannot be considered inventive (PCT Article 33(3)), for the following reasons:

Document D4 discloses the compound claimed in claim 2, that is to say, carboxyeosin diacetate succimidyl esters, as PMCA (plasma membrane calcium-ATPase) inhibitor.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

A person skilled in the art familiar with the fact that PMCA inhibitors have a contraceptive effect and that 5- and 6-carboxyeosin diacetate succimidyl esters are PMCA inhibitors would use the claimed compounds to achieve a contraceptive effect. Consequently, it would be obvious to a person skilled in the art to use the compounds 5- and 6-carboxyeosin diacetate succimidyl esters, which display an PMCA inhibiting activity, as contraceptives.

The use of an inhibitor of the isoform PMCA4 of ATPase can be considered inventive only if it can be shown to have surprising effects.

Consequently, a person skilled in the art would combine all the features disclosed in documents D2, D3 and D4 in order to solve the problem of interest, without thereby being inventive. Consequently, claims 1, 2, 5-7, 9 and 10 are not inventive (PCT Article 33(3)).

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/007168

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/*month*/year)	Filing date (day/*month*/year)	Priority date (valid claim) (*day*/month/*year*)

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/*month*/year)	Date of written disclosure referring to non-written disclosure (*day*/month/*year*)

See Supplemental Box

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Box III.1

1.1 No international preliminary examination report is established for aspects of the application in respect of which no search was carried out. Consequently, the international preliminary examination report was directed to those parts of the claims which correspond to the original first invention searched, that is to say, claims 1, 2 and 5-10 (in part).

1.2 The valid claim 1 concerns a group of compounds, each characterized by their pharmacological profile, that is to say, their activity as "inhibitors of plasma membrane calcium-ATPase (PMCA), wherein the inhibitor targets the isoform PMCA4".

The valid claim 9 concerns a group of compounds, each characterized by their pharmacological profile, that is to say, their activity as conventional contraceptives.

A relationship between structural features of these compounds and their activity is not defined. In the absence of a disclosure of this kind, without a structural definition, a person skilled in the art would not know how to produce and use such compounds. Moreover, it is not possible to determine whether a given compound (different from the one disclosed in the application) is encompassed by the scope of protection sought.

Supplemental Box

It would be unreasonable to acknowledge undefined compounds for the claimed activity.

Consequently, the international preliminary examination report was established in respect of those parts of the claim which were searched and which are considered clear, supported or disclosed in the above sense, that is to say, the parts concerning the products 5- and 6-carboxyeosin diacetate-succimidyl ester.

1.3 Claims 1-2 and 5-7 refer to a contraceptive method for the human or animal body. Consequently, no report is established in respect of the industrial applicability of the subject matter of these claims (PCT Article 34(4)(a)(i)).